HHS Public Access

Author manuscript

BJOG. Author manuscript; available in PMC 2015 May 18.

Published in final edited form as:

BJOG. 2012 September ; 119(10): 1180–1190. doi:10.1111/j.1471-0528.2012.03393.x.

The effect of different alcohol drinking patterns in early to mid-pregnancy on child's intelligence, attention and executive function

Ulrik Schiøler Kesmodel[1,2], **Jacquelyn Bertrand**[3], **Henrik Støvring**[4], **Bradley Skarpness**[5], **Clark H Denny**[3], **Erik Lykke Mortensen**[6], and **the Lifestyle During Pregnancy Study Group**[*]

[1]Department of Public Health, Section of Epidemiology, Aarhus University, Denmark

[2]Department of Obstetrics and Gynaecology, Aarhus University Hospital, Aarhus, Denmark

[3]Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA

[4]Department of Public Health, Section of Biostatistics, Aarhus University, Denmark

[5]Battelle, Columbus, Ohio, USA

[6]Institute of Public Health and Center for Healthy Aging, University of Copenhagen, Denmark

Abstract

Objective—To conduct a combined analysis of the estimated effects of maternal average weekly alcohol consumption and any binge drinking in early to mid-pregnancy on general intelligence, attention, and executive functions in five-year old children.

Design—Follow-up study.

Setting and population—1,628 women and their children sampled from the Danish National Birth Cohort.

Methods—Participants were sampled based on maternal alcohol consumption during early pregnancy. At age five, the children were tested for general intelligence, attention and executive

Correspondence to: Ulrik Schiøler Kesmodel, Department of Public Health, Section of Epidemiology, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark.

[*]The Lifestyle During Pregnancy Study Group

Leiv S Bakketeiga, Coleen A Boyleb, Mary E Cogswellb, Hanne-Lise F Eriksenc, Jakob Groved, Tina Kilburnc, Nils Inge Landrøe, Åshild Skogerbøf, Mette Underbjergc+g, Theresa Wimberleyh

Disclaimer: The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflicts of interest: none

Contributions

Ulrik Schiøler Kesmodel, Jacquelyn Bertrand, Erik Lykke Mortensen, Leiv S Bakketeig, Niels Inge Landrø, Tina Kilburn and Mette Underbjerg contributed to the design of the Lifestyle During Pregnancy Study. Ulrik Schiøler Kesmodel, Jacquelyn Bertrand, Henrik Støvring [3], Bradley Skarpness, and Erik Lykke Mortensen wrote the first draft of the manuscript in collaboration, and Henrik Støvring and Bradley Skarpness were responsible for the statistical analyses. All authors contributed to the interpretation of the results and with critical comments and revisions of the manuscript.

Ethics

The study was approved by the DNBC Board of Directors, the DNBC Steering committee, the regional Ethics Committee, the Danish Data Protection Agency, and the Institutional Review Board at the Centers for Disease Control and Prevention. Signed informed consent was obtained for the LDPS.

function. The three outcomes were analyzed together in a multivariate model to obtain joint estimates and p-values for the association of alcohol across outcomes. The effects of low-moderate alcohol consumption and binge drinking in early pregnancy were adjusted for a wide range of potential confounders.

Main outcome measures—Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R), the Test of Everyday Attention for Children at Five (TEACh-5), the Behavior Rating Inventory of Executive Functions (BRIEF).

Results—Multivariate analyses showed no statistically significant effects of average weekly alcohol consumption or any binge drinking, individually or in combination. These results replicate findings from separate analyses of each outcome variable.

Conclusion—The present study contributes comprehensive methodological and statistical approaches that should be incorporated in future studies of low-moderate alcohol consumption and binge drinking during pregnancy. Further, since no safe level of drinking during pregnancy has been established, the most conservative advice for women is not to drink alcohol during pregnancy. However, the present study suggests that small amounts consumed occasionally may not present serious concern.

Keywords

Prenatal exposures; low-moderate alcohol consumption; binge drinking; neurodevelopmental effects; multiple outcome analyses; intelligence; attention; executive function; WPPSI-R; TEACh-5; BRIEF

Introduction

High prenatal exposure to alcohol has consistently been associated with adverse effects on neurodevelopment. Areas such as intelligence,[1;2] attention[3;4] and executive functions[5;6] have been found to be particularly vulnerable. Less is known about the effects of low to moderate, weekly average consumption levels. In addition to absolute amounts of alcohol exposure in utero, differences in maternal drinking patterns also may impact these areas of functioning in young children.[7;8]

Individual alcohol consumption may be described by four components: Frequency, quantity, variability and timing.[9] During pregnancy, women are usually asked simply how many drinks they drink on average per day[10;11] or per week,[12;13] although other variants are also used.[9;14] However, a single measure of overall consumption cannot give a sufficiently detailed picture of consumption pattern. A recurrent problem in most previous studies on prenatal alcohol exposure is that, with few exceptions, they have obtained only one estimate of consumption at one point in time during pregnancy. Binge drinking[15] or any other measure of variability or peak exposure[16] has been considered in only few studies.[8]

Studies on moderately high alcohol intake during pregnancy have yielded somewhat inconsistent findings, showing sporadic associations with cognitive function. A few studies of children of mothers with intake of 2–3 drinks per day have reported lower general intelligence compared with children whose mothers had no intake,[17] but several other

studies have failed to detect such an association.[18] Attention deficits and dysfunctions are among the most commonly reported adverse effects of maternal alcohol consumption during pregnancy, with a few studies showing an association between low levels of prenatal alcohol exposure and attention problems.[19] Finally, deficits in executive functioning have been found consistently for children with high levels of prenatal alcohol exposure,[20] but no previous studies have investigated associations between low, weekly exposure levels and executive functions.

Using data from the Lifestyle During Pregnancy Study (LDPS), a large cohort of preschool children, recent studies have examined the effects of low to moderate, average weekly levels of prenatal alcohol exposure and any binge drinking on child IQ,[21;22] attention[23] or executive functioning[24] independently, without observing systematic, significant effects at less than daily intake levels. However, these three cognitive functions are not independent characteristics of the individual child By combining multiple outcomes in a single analysis, the results would reflect not only intercorrelations among the three outcomes, but also associations between the combination of outcomes and exposure variables as well as included covariates such as postnatal factors. Further, in spite of the lack of systematic effects of alcohol exposure observed for individual outcomes, analyses of multiple outcomes might show more consistent and precisely estimated effects of maternal alcohol consumption during pregnancy.

The LDPS is particularly well suited to address both multiple exposure patterns as well as multiple outcomes: participants were prospectively sampled from a homogeneous, low risk population,[25] and systematically sampled according to average number of drinks per week as well as timing of binge drinking during early pregnancy. It included comprehensive assessment of multiple domains of child neurodevelopmental functioning and a broad range of covariates were available.

The specific aim of the present study was to conduct a combined, multiple outcome analysis of the effects of maternal average weekly alcohol consumption and binge drinking in early to mid-pregnancy on the combination of outcomes consisting of general intelligence, attention, and executive functions in five-year old children using the large and well-characterized LDPS-sample.

Methods

Sample

The LDPS has been described in detail elsewhere, including the sampling frame.[26] Briefly, participants were drawn from the Danish National Birth Cohort (DNBC),[25] a prospective cohort study of 101,042 women and their children. Women in the DNBC were recruited from 1997–2003, at their first antenatal visit at a general practitioner (routinely the first contact to a healthcare practitioner for a pregnant woman). Participating women represent 60% of those invited and approximately 30% of all pregnant women in Denmark in the enrolment period.[26]

Based on their alcohol-drinking pattern before and during pregnancy, a total of 3478 women were sampled from the DNBC and invited to participate in the LDPS between 2003 and 2008.[26] Although the focus was on women with low average weekly alcohol consumption (defined in this study as 1–4 drinks per week), oversampling was done for women with moderate and higher levels of alcohol consumption (defined in this study as 5–8 drinks and ≥9 drinks per week), including binge drinking to ensure adequate representation.[26] Participants who did not drink during pregnancy were included as the unexposed reference group. The sample design and sampling fractions are displayed in Table 1. Women sampled on the basis of pre-pregnancy alcohol intake were not included in these analyses (category 6 and 7 in Table 1, n=289), leaving 3189 invited, of whom 1628 were tested. Children in the LDPS were 60–64 months of age (mean= 5.22 years, range = 5.00–5.34) at follow-up. Fifty two percent of the children were boys.

Exclusion criteria for the LDPS were mother's or child's inability to speak Danish, impaired hearing or vision of the child to the extent that the test session could not be performed, child from a multiple pregnancy, and congenital disorders likely to cause mental retardation (e.g. Down syndrome).[26]

5-year follow-up procedures

Sampled mothers were invited to participate in the study by letter approximately 4–6 weeks (mean=5.8, SD=0.7) before their child's fifth birthday. A self-administered questionnaire was mailed to the participating mothers asking about their child's general postnatal health and development as well as maternal and paternal postnatal lifestyle characteristics (available on request from the authors).

Child outcome measures and maternal IQ were obtained during a 3-hour assessment at a university or health clinic site.[26] Test sites were located in Copenhagen, Aarhus, Odense and Aalborg to minimize travel distance for all participants. All assessments were administered by ten trained psychologists blinded to the child's exposure status. Test procedures were standardized in detail. Measures were administered in a fixed order. Reliability across psychologists was assessed periodically and remained high throughout data collection.[26] Tester differences were taken into account by the inclusion of an indicator variable in the statistical analyses representing individual testers.

While the psychologists tested the children, mothers were administered the Raven IQ test and completed the Behavior Rating Inventory of Executive Function (BRIEF) Parent Form (see below). The BRIEF Teacher Form was mailed to the kindergarten a few weeks before the planned test date. Because of lower participation by teachers, only results for the parents' BRIEF are reported in these analyses.

Measures

Exposure variables—Information on alcohol consumption during the index pregnancy was extracted from the first DNBC interview administered prenatally.[27] For women participating in the follow up, the median week of gestation for completing the interview was 17 weeks (range 7–39 weeks) and 61.6% (n=1002) completed it between 14 to 20

weeks. By week 20 of gestation, 75% of women had completed the interview. The questions and procedures used have been shown to yield valid (relative to other methods) and reliable information among pregnant Danish women.[15;28;29] For average alcohol intake per week, questions assessed the average number of drinks per week of beer, wine, and spirits that the pregnant woman consumed at the time of the prenatal interview. The definition of a drink followed the definition from the Danish National Board of Health (DNBH), one standard drink being equal to 12 grams of pure alcohol. Prenatal maternal average alcohol intake was a priori categorized into four groups (0, 1–4, 5–8, ≥9 drinks/week). Information on binge episodes was obtained from the same prenatal interviews. Binge episodes were defined as intake of ≥5 drinks on a single occasion. The obtained information also included data on the number of binge episodes as well as the timing (gestational week) of these episodes up until the time of the interview, thus covering nearly the first half of pregnancy. Because the majority of women (69%) reported only one binge episode, we categorized binge into any versus no binge for this analysis. Some women reported one or more binge episodes during the early weeks of pregnancy, although their average number of drinks per week at the time of interview was zero. These women were classified accordingly as consuming an average of zero drinks at the time of interview, but with one or more previous binge episodes.

Outcome variables—The LDPS included a comprehensive neuropsychological assessment which has been described elsewhere.[26] This analysis includes a standard clinical intelligence test, a project-developed test of attention validated with a separate group of Danish preschoolers, and a standard clinical measure of executive functioning for preschoolers.

Intelligence was assessed with the Wechsler Primary and Preschool Scales of Intelligence-Revised (WPPSI-R),[30] one of the most widely used, standardized tests of intelligence for children of three to seven years. The WPPSI-R was the version available in Danish at the time of initiation of the study. It consists of five verbal subtests and five performance (non-verbal) subtests from which verbal (VIQ), performance (PIQ), and full scale (FSIQ) IQs are derived. To reduce the length of the test session, we used a short form including three verbal (Arithmetic, Information and Vocabulary) and three performance subtests (Block Design, Geometric Design and Object Assembly). Standard procedures were used to prorate IQs from the shortened forms of the tests.

Since no Danish WPPSI-R norms were available at the time of the study, Swedish norms were used to derive scaled scores and IQs.[21]

Attention was measured using the recently developed Test of Everyday Attention for Children at Five (TEACh-5).[31] The measure is a downward extension for younger children based on the model proposed by Posner and Petersen.[32–35] Detailed description of development of the TEACh-5, validation and its psychometric properties are provided elsewhere.[31] For the present analyses both selective attention and sustained attention were assessed. Briefly, selective attention was composed of a non-verbal cancellation task plus an auditory task of listening for a specific target among distracters. Sustained attention was composed of an auditory task of counting the number of times a target sound was produced

at various rates of presentation plus a visual motor task of drawing a line as slowly as possible.

The number correct and the log-transformed scores (auditory target identification and drawing a line) were first standardized to a mean of 0 and a SD of 1. The mean of the four standardized scores were then calculated and re-standardized to a mean of 0 and a SD of 1 for use in the statistical analyses.

The Behavior Rating Inventory of Executive Function (BRIEF) is an 86 item questionnaire that assesses executive function behaviors in the home as rated by the mother and day care environments as rated by staff. Several aspects of executive functioning are evaluated by the BRIEF, but only data on the three standardized index scores Behavioral Regulation Index (BRI), Metacognition Index (MI) and Global Executive Composite (GEC)[36] are presented in this paper.

A translated version of the BRIEF was used (Danish Psychological Publishers) with minor adjustments for Danish preschool children. No Danish BRIEF norms were available at the time of the study, and consequently we constructed our own Danish norms. A normalizing *T*-score transformation for the observed BRIEF scores was computed, with higher scores indicating more difficulty.[37] The BRIEF is a highly reliable instrument: For the two index scores and the overall score, Cronbach's α based on the full LDPS sample was in the range of 0.91–0.96 for the parent version of the questionnaire.

Covariates—The analysis examined a number of potential confounders obtained from the prenatal interview as well as several collected during the five-year old assessment. From the prenatal interview the following covariates were included: parity (0, 1, ≥2); prenatal maternal smoking (yes/no); maternal pre-pregnancy BMI (weight in kg/(height in m)^2). From the 5-year follow-up, the following variables were included: length of parental education in years (the average educational length for the two parents or length of maternal education if information on the father was unavailable, treated as a continuous measures); marital status (single either at the prenatal interview or at follow-up/married or cohabitating at both); postnatal parental smoking (yes, if at least one of the parents smoked in the home/no, if otherwise); child health status (yes, if presence of major medical conditions or regular use of prescription medications that might influence test performance (including epilepsy, syndromes [e.g. neurofibromatosis type 1], congenital toxoplasmosis and hypothyroidism; and medicines for asthma and allergy, attention deficit hyperactivity disorder, epilepsy and respiratory conditions)/no, if otherwise); dichotomized family/home environment index (yes, if presence of two or more of the following seven adverse conditions: not living with a biological parent, changes in caregiver, day care before age 3 years, ≥14 days residing continuously outside of home, breakfast irregularity, maternal depression and parental alcohol use at the time of follow-up above the maximum recommended level by the DNBH of 14 drinks per week for women and 21 drinks per week for men/no, if otherwise); measured hearing ability on the test day (impaired/not impaired); measured vision ability on the test day (impaired/not impaired).

Maternal IQ was assessed at the follow-up examination using two verbal subtests (Information and Vocabulary) from the Wechsler Adult Intelligence Scale[37] (WAIS) and the Raven's Standard Progressive Matrices.[38] Raw scores were standardized based on the results from the full sample and weighted equally in a combined score that was re-standardized to an IQ scale with a mean of 100 and an SD of 15.

Maternal age was obtained directly from the unique Danish personal identification number, as was gender of child and age of child at testing. Birth weight (g) and gestational age (days) were obtained from the Danish Birth Registry.

Statistical analysis

Missing information—The final set of data had a number of missing values in each outcome variable which ranged from 8 (0.5%) for FSIQ to 249 (15.3%) for TEACh-5, mainly due to e.g. motivational factors, lack of understanding test premises, or lack of ability to perform the test. Among covariates, the number of missing values ranged from 2 (0.1%) for the hearing variable to 33 (2.0%) for maternal pre-pregnancy BMI. As missing values were most frequent in outcome variables, we report the pattern of missing values for these individually together with an overall measure of missingness for covariates (i.e. whether or not at least one covariate had a missing value) in Table 2.

Numerical analytic approach—The primary analysis of this paper is a multivariate analysis of multiple neurodevelopmental outcomes[39] with various alcohol measures as exposures and with adjustments for confounders. Each child attempted to complete the full battery of tests, and these outcomes were expected to be correlated. This correlation across the variance-covariance matrix, in general, can be shown to reduce the standard errors of the estimates of the model parameters over the analyses of single outcomes. The multivariate model can be analyzed with standard statistical software, if the dataset is complete without any missing values. As both individual covariate values and individual outcome values were missing in our dataset, we addressed the missing data problem by using multiple imputation, which yields unbiased estimates if the data are missing at random (MAR).[40;41] This is not the case for an analysis based only on individuals with complete information for the relevant variables (complete case analysis). The first step in multiple imputations generates $m > 1$ complete data sets where in each data set, the missing data have been replaced by imputed values based on predictive distributions for each missing value. In the second step, each of the completed data sets is analyzed by standard methods, and the results from the *m* analyses are combined to produce a single set of inferences that includes the variability associated with the missing data. We used Stata 11 to generate 200 imputed – and hence complete – datasets, which we then subjected to the ordinary multivariate analysis (PROC MIXED, SAS 9.2). A large number of imputed datasets, n=200, was used since we included several parameters in some of the analyses. PROC MIXED was chosen over Stata's xtmixed command, since it allowed weighting with sampling fractions and use of robust variance estimation.

All analyses were weighted by sampling fractions with robust variance estimation to account for the complex stratified sampling design, and all statistical tests were two-sided and

declared significant at 5% level. All estimates include 95% confidence intervals. For correlation coefficients we used bootstrap to estimate their confidence intervals.

Data analyses—Parental education, maternal IQ, prenatal maternal smoking, the child's sex and age at testing, and tester were considered core confounders essential to any model of child neurodevelopment and included as covariates in an initial model. A final model included the core confounders and in addition the following a priori potential confounders were chosen on the basis of previous associations described in the literature: Parity, maternal marital status, maternal age, pre-pregnancy BMI, home environment, postnatal parental smoking, health status, and hearing and vision abilities.

Further, potential interactions with binge drinking and average alcohol consumption were assessed for child's sex, parental education (being strongly associated with cognitive ability) and maternal smoking during pregnancy (being strongly associated with alcohol use).

The study was approved by the DNBC Board of Directors, the DNBC Steering committee, the regional Ethics Committee, the Danish Data Protection Agency, and the Institutional Review Board at the Centers for Disease Control and Prevention. Signed informed consent was obtained for the LDPS.

Results

In this sample, the unadjusted mean maternal age was 30.9 (SD 4.4) years, 50.1% were primiparous, 12.1% single, parental education (median number of years, 10/90 percentile) was 13.0 years (11.0/16.0), 31.4% reported smoking during pregnancy.[21] Among binge drinkers, 69% reported one episode in early pregnancy, the remainder 2–12 episodes. The median weekly number of alcohol drinks was 1 drink for the 1–4 consumption category, 5 drinks for women in the 5–8 consumption category and 10 drinks for women in the ≥9 consumption categories. Among children, mean birth weight was 3602 (SD 516) grams and median gestational age at birth 281 days and the 10/90 percentiles were 267/293 days. No substantial or statistically significant differences were observed between participants and non-participants for the alcohol exposure variables and the various covariates.[21;22]

Table 2 shows the pattern of missing data with respect to the three outcomes and the included covariates. The complete case analysis was based on 1337 mother-child pairs with complete data on all outcomes and covariates. The imputed data set included 1628 pairs. There was relatively little missing data in this sample. The majority of missing data involved one outcome (n=231) or one or more covariates (n=39). Among outcome measures, data for the TeaCh-5 was most likely to be missing and among covariates data for BMI was most likely to be missing.

Table 3 shows the observed correlations among the three outcomes for the 1337 cases with complete information. The table also presents the partial correlations adjusted for alcohol exposure and core confounders for both the complete case analysis and the analysis based on imputation sample. The correlation between IQ and the TEACh-5 mean score was moderately strong while the correlations between these two measures and the BRIEF GEC

index were significant, but relatively weak. The latter two correlations were negative because low GEC scores correspond to better rating of the child's performance.

Table 4 shows results of the multivariate analysis for the imputed case analyses of the effects of average consumption and binge drinking. For the unadjusted analysis, the overall multivariate test was clearly not significant (p = 0.44), nor were separate multivariate tests of average alcohol intake and binge drinking (p = 0.63 and 0.28 respectively). The results of the multivariate analysis were corroborated by the pattern of insignificant results in the unadjusted univariate analyses.

Neither the unadjusted analysis nor the adjusted analyses showed any significant multivariate tests. For the model adjusting for core confounders the p-value for the overall test of alcohol effects was 0.80 and for average alcohol consumption and binge drinking 0.65 and 0.90, respectively. Thus, a very consistent pattern of insignificant effects of both average consumption and binge drinking was observed. The point estimates of effects were little affected by adjustment for confounders. All models showed insignificant negative effects of ≥9 drinks/week consumption on WPPSI-R IQ and TEACh-5 attention scores, while the effect on BRIEF were mixed for this group.

Linear and quadratic models were fit to the outcome variables across increased levels of average number of drinks per week. Neither model was significant (data not shown).

Multivariate tests of the interaction between average consumption and binge drinking were not significant in any of the statistical models (complete case: p=0.60, multiple imputed data: p=0.96). This was also the case for multivariate tests of the potential interaction of gender, parental education and prenatal smoking with average consumption and with binge drinking.

Supplementary multivariate analyses were conducted with the following outcome variables analyzed jointly: Verbal and Performance IQ, TEACh-5 selective and sustained mean scores, BRIEF BRI index and BRIEF MI index. No multivariate tests were significant, and thus these analyses affirmed the results of the main analyses.

The complete data case analysis overall gave the same results as the imputed case, but some of the estimates were slightly different (data not shown). Generally, the results based on the imputed dataset were comparable to the results of the complete case analysis, but it is worth noting that most of the p-values for the analysis based on the imputed dataset were higher than the corresponding p-values for the complete case analyses. For the WPPSI-R and the TEACh-5, the complete dataset based on multiple imputation showed larger effect estimates for the ≥9 drinks/week consumption group, but also wider confidence intervals.

Discussion

We found no significant association of maternal low-moderate average weekly alcohol consumption and any binge drinking during early to mid-pregnancy with neurodevelopment of children at age 5 years. This finding was based on comprehensive methodological and statistical approaches applying multivariate techniques together with state-of-the-art

handling of missing values that maximized the chance of detecting a difference between children who had prenatal exposure to alcohol and children who did not. Further, potential findings were investigated across and among the most salient neurodevelopmental outcomes previously associated with prenatal alcohol exposure. To our knowledge, no previous studies on alcohol use during pregnancy have performed such multivariate analyses, analyzing several outcomes together within the same model.

Results from this study replicate the findings for each individual outcome reported elsewhere[21–24] and also replicate some previous studies which investigated associations between average low-moderate alcohol consumption in the range investigated in this study or any binge drinking and the individual cognitive and outcomes.[18;42;43] Further, this study provides important information regarding the lack of interactions between exposure patterns (average intake vs. binge drinking) as well as the interactions among outcomes. In addition, this study provides methodological and statistical guidance for future studies of this issue in that it describes a method for analyzing both average weekly consumption of alcohol and binge drinking simultaneously to investigate possible interactions between these drinking patterns. Finally, this study indicates that multiple outcomes should be included in studies of neurodevelopment since in utero exposure to alcohol may result in a diverse pattern of cognitive strengths and weaknesses that may only be detected across outcome measures for any particular sample of children.

In addition to these general findings, results of our analyses also revealed substantially higher unadjusted and adjusted correlations between measures of IQ and the composite attention score than between these cognitive measures and the parent rating of executive functions. The reason for this pattern of correlations may be due to differing methods of data collection. For IQ and attention the child was tested directly by a trained psychologist. Executive function was assessed by parent observation or interpretation of daily behavior as related to these cognitive skills. However, all correlations were high enough to make the multiple outcome analyses meaningful. Our data showed a somewhat higher correlation between intelligence and attention scores than is usually observed between measures of these domains,[44] but this may reflect the fact that we used a composite (and presumably more reliable) measure of attention.

The strengths of the LDPS data include use of a large prospective cohort, inclusion of a large number of covariates (especially maternal IQ and parental education),[18;45] and a sample drawn from a relatively middle-class homogenous population of women. Additionally, inclusion of multiple exposure patterns allowed for investigation of possible interactions between these patterns and outcomes. Also, the imputation method allowed for analysis of the total sample potentially adding to statistical power and diminishing bias. This increased power maximized the opportunity to detect subtle effects and reject the null hypothesis.

Like all research studies, limitations were encountered. A null effect always raises the possibility that the study design or measures chosen simply failed to detect a true effect. This is an especially salient point when effects are small or subtle, such as would be expected in this case. Also, because of the many associations between drinking habits,

individual and social risk factors for offspring cognitive/behavioral development,[46–48] residual confounding is a possibility despite the broad range of covariates included. However, the presented analyses included outcomes from at least two distinct developmental domains (IQ/attention and executive function) which are unlikely to be associated with exactly the same observed and unobserved confounders, and thus the similar results for all three outcomes substantiate the finding of no significant alcohol effects. Power to detect the very subtle neurodevelopmental effects under investigation should be considered in this study. Although deviations of half a standard deviation would be the smallest functionally meaningful effect, the small sample sizes at the individual average weekly by binge category levels may have precluded detection of such subtle effects, (especially in the 9+ consumption category).[26] We previously calculated the minimum detectable RR in our samples as 1.5, 1.7, and 3.5 for the low (1–4 d/week), moderate (5–8 d/week) and high (9+ d/week) categories, respectively.

In general, information bias, in particular misclassification, is a possibility in studies of alcohol during pregnancy.[49] Even so, with several exposure categories, non-differential misclassification due to underreporting could be expected to lead to bias away from the null value.[49] Compared to other studies, underreporting in this study may be reduced because we used methods shown to yield valid and reliable information among pregnant Danish women[28;29;50] and because consumption of small amounts of alcohol during pregnancy generally was not considered to be problematic in Denmark during the time of data collection.[51;52] Since information on alcohol use reflected the time period of study enrollment, which varied from 7 weeks to 39 weeks, impact on neurodevelopment may have been diluted if such exposure was sensitive to a specific time period in gestation.

It should be noted that on average, the exposure represents the lower tail of the distribution for the average consumption categories, suggesting that these findings speak mostly to levels of less than one drink per day.

While the 51% participation rate for this study is quite good for studies of this nature, the potential impact of differential participation should be considered. It is reassuring that participants and non-participants did not differ substantially on key covariates, nonetheless it remains possible that participation may have been associated with both alcohol status and child neurodevelopmental functioning (either positive or negative). Such selection bias could potentially mask an apparent association with maternal alcohol use.

Finally, all studies of neurodevelopment must be considered within the framework of child development. Effects that are detectable at younger ages may or may not be detectable at older ages depending on the specific construct under study. In addition, as children develop, cognition diversifies and environmental factors exert influence, and consequently some effects may only be detectable at older ages.[53] The LDPS outcomes were assessed only when the participants were five years old, a relatively early stage in the development of intelligence, attention and executive functioning. However, at least one study of effects of alcohol on IQ suggested that effects observed in early childhood may be diluted in later childhood and adolescence.[54] If this is a general phenomenon, it is unlikely that future follow-ups of our sample will show effects of maternal low-moderate average weekly

consumption and binge drinking on offspring intelligence, attention and executive functions. However it is important that studies of older children be conducted to fully address this possibility.

The lack of significant findings suggests that any effects of low average weekly alcohol consumption or any episodes of binge drinking in the first half of pregnancy on these specific aspects of child neurodevelopment may be small. To date, the scientific literature, including the present study, does not establish a safe level of alcohol consumption during pregnancy. Since alcohol is a known teratogen, it remains the most conservative advice for women to abstain from alcohol during pregnancy. However, small amounts consumed occasionally in pregnancy do not appear to pose serious issues for these three areas of neurodevelopment. Despite these findings, additional large scale studies that further investigate the possible effects low to moderate alcohol use during pregnancy may have across childhood should be conducted using comprehensive methodological and statistical approaches similar to those described for this study.

Acknowledgments

Funding

This study was supported primarily by the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA. Additional support was obtained from The Danish National Board of Health, the Lundbeck Foundation, Ludvig & Sara Elsass' Foundation, the Augustinus Foundation, and Aase & Ejnar Danielsen's Foundation

The Danish National Research Foundation has established the Danish Epidemiology Science Centre that initiated and created the Danish National Birth Cohort. The cohort is furthermore a result of a major grant from this Foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Augustinus Foundation and the Health Foundation.

The authors would like to thank all the participants for their time and efforts as well as Dr. Tom Manly for his contribution to the development of the TEACh-5 test.

References

1. Bailey BN, Delaney-Black V, Covington CY, Ager J, Janisse J, Hannigan JH, et al. Prenatal exposure to binge drinking and cognitive behavioral outcomes at age 7 years. Am J Obstet Gynecol. 2004; 191(3):1037–1043. [PubMed: 15467586]
2. Mukherjee RA, Hollins S, Turk J. Fetal alcohol spectrum disorder: an overview. J R Soc Med. 2006; 99(6):298–302. [PubMed: 16738372]
3. Coles CD, Platzman KA, Lynch ME, Freides D. Auditory and visual sustained attention in adolescents prenatally exposed to alcohol. Alcohol Clin Exp Res. 2002; 26(2):263–271. [PubMed: 11964567]
4. Streissguth AP, Barr HM, Sampson PD, Parrish Johnson JC, Kirchner GL, Martin DC. Attention, distraction and reaction time at age 7 years and prenatal alcohol exposure. Neurobehav Toxicol Teratol. 1986; 8(6):717–725. [PubMed: 3808187]
5. Connor PD, Sampson PD, Bookstein FL, Barr HM, Streissguth AP. Direct and indirect effects of prenatal alcohol damage on executive function. Developmental Neuropsychology. 2000; 18(3):331–354. [PubMed: 11385829]
6. Noland JS, Singer LT, Arendt RE, Minnes S, Short EJ, Bearer CF. Executive functioning in preschool-age children prenatally exposed to alcohol, cocaine, and marijuana. Alcohol Clin Exp Res. 2003; 27(4):647–656. [PubMed: 12711927]
7. Henderson J, Gray R, Brocklehurst P. Systematic review of effects of low-moderate prenatal alcohol exposure on pregnancy outcome. BJOG. 2007; 114:243–252. [PubMed: 17233797]

8. Henderson J, Kesmodel U, Gray R. Systematic review of the fetal effects of prenatal binge-drinking. Journal of Epidemiology and Community Health. 2007; 61(12):1069–1073. [PubMed: 18000129]
9. Kesmodel, U. Self-reported intake of alcohol: methods and approaches. In: Preedy, VR.; Watson, RR., editors. Comprehensive handbook of alcohol related pathology. London: Elsevier; 2004. p. 1367-1382.
10. Harlap S, Shiono PH. Alcohol, smoking, and incidence of spontaneous abortions in the first and second trimester. Lancet. 1980; 2(8187):173–176. [PubMed: 6105340]
11. Lazzaroni F, Bonassi S, Magnani M, Calvi A, Repetto E, Serra F, et al. Moderate maternal drinking and outcome of pregnancy. Eur J Epidemiol. 1993; 9(6):599–606. [PubMed: 8150062]
12. da Costa Pereira A, Olsen J, Ogston S. Variability of self reported measures of alcohol consumption: implications for the association between drinking in pregnancy and birth weight. J Epidemiol Community Health. 1993; 47(4):326–330. [PubMed: 8228772]
13. Kesmodel U, Olsen SF, Secher NJ. Does alcohol increase the risk of preterm delivery? Epidemiology. 2000; 11(5):512–518. [PubMed: 10955402]
14. Windham GC, Fenster L, Swan SH. Moderate maternal and paternal alcohol consumption and the risk of spontaneous abortion. Epidemiology. 1992; 3(4):364–370. [PubMed: 1637900]
15. Kesmodel U. Binge drinking in pregnancy - frequency and methodology. Am J Epidemiol. 2001; 154(8):777–782. [PubMed: 11590091]
16. Walpole I, Zubrick S, Pontre J. Is there a fetal effect with low to moderate alcohol use before or during pregnancy? J Epidemiol Community Health. 1990; 44(4):297–301. [PubMed: 2277251]
17. Streissguth AP, Barr HM, Sampson PD, Darby BL, Martin DC. IQ at age 4 in relation to maternal alcohol use and smoking during pregnancy. Dev Psychol. 1989; 25(1):3–11.
18. Alati R, Macleod J, Hickman M, Sayal K, May M, Smith GD, et al. Intrauterine exposure to alcohol and tobacco use and childhood IQ: Findings from a parental-offspring comparison within the Avon Longitudinal Study of Parents and Children (ALSPAC). Pediatr Res. 2008; 64(6):659–666. [PubMed: 18670372]
19. Coles CD, Platzman KA, Raskind-Hood CL, Brown RT, Falek A, Smith IE. A comparison of children affected by prenatal alcohol exposure and attention deficit, hyperactivity disorder. Alcohol Clin Exp Res. 1997; 21(1):150–161. [PubMed: 9046388]
20. Chasnoff IJ, Wells AM, Telford E, Schmidt C, Messer G. Neurodevelopmental functioning in children with FAS, pFAS, and ARND. J Dev Behav Pediatr. 2010; 31:192–201. [PubMed: 20375733]
21. Eriksen H-LF, Mortensen EL, Kilburn TR, Underbjerg M, Bertrand J, Støvring H, et al. The effects of low to moderate prenatal alcohol exposure on IQ in 5-year-old children. BJOG. 2011
22. Kesmodel US, Eriksen H-LF, Underbjerg M, Kilburn TR, Støvring H, Wimberley T, et al. The effect of alcohol binge drinking in early pregnancy on general intelligence. BJOG. 2011
23. Underbjerg M, Kesmodel US, Landrø NI, Bakketeig LS, Grove J, Wimberley T, et al. The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on selective and sustained attention in five-year-old children. BJOG. 2011
24. Skogerbø Å, Kesmodel US, Wimberley T, Støvring H, Bertrand J, Landrø NI, et al. The effects of low to moderate alcohol consumption and binge drinking ni early pregnancy on executive function in five-year-old children. BJOG. 2011
25. Olsen J, Melbye M, Olsen SF, Sorensen TI, Aaby P, Andersen AM, et al. The Danish National Birth Cohort--its background, structure and aim. Scand J Public Health. 2001; 29(4):300–307. [PubMed: 11775787]
26. Kesmodel US, Underbjerg M, Kilburn TR, Bakketeig LS, Mortensen EL, Landrø NI, et al. Lifestyle during pregnancy: Neurodevelopmental effects at 5 years of age. The design and implementation of a prospective follow-up study. Scand J Public Health. 2010; 38(2):208–219. [PubMed: 20064917]
27. The Danish National Birth Cohort. Code books for interviews 1–4. 2010. http://www.ssi.dk/English/R%20and%20D/Epidemiology/DNBC/For%20researchers/Data%20available/Interviews%201%20-%204.aspx
28. Kesmodel U, Olsen SF. Self-reported alcohol intake in pregnancy: comparison between four methods. J Epidemiol Community Health. 2001; 55(10):738–745. [PubMed: 11553658]

29. Kesmodel U, Frydenberg M. Binge drinking during pregnancy--is it possible to obtain valid information on a weekly basis? Am J Epidemiol. 2004; 159(8):803–808. [PubMed: 15051590]
30. Wechsler, D. Manual for the Wechsler Preschool and Primary Scale of Intelligence - Revised. Sidcup, Kent: The Psychological Corporation; 1990. UK edition ed
31. Underbjerg, M. Prenatal exposure to low-moderate doses of alcohol and binge drinking: Effects on offspring's attention functions. Faculty of Health Sciences, University of Aarhus; Denmark: 2008.
32. Manly T, Anderson V, Nimmo-Smith I, Turner A, Watson P, Robertson IH. The differential assessment of children's attention: the Test of Everyday Attention for Children (TEA-Ch), normative sample and ADHD performance. J Child Psychol Psychiatry. 2001; 42(8):1065–1081. [PubMed: 11806689]
33. Posner MI, Petersen SE. The attention system of the human brain. Ann Rev Neurosci. 1990; 13:25–42. [PubMed: 2183676]
34. Posner, MI.; Raichle, ME. Images of mind. New York: Freeman; 1994.
35. Robertson IH, Ward T, Ridgeway V, Nimmo-Smith I. The structure of normal human attention: The Test of Everyday Attention. J Int Neuropsychol Soc. 1996; 2(6):525–534. [PubMed: 9375156]
36. Gioia GA, Isquith PK, Guy SC, Kenworthy L. Behavior rating inventory of executive function. Child Neuropsychol. 2000; 6(3):235–238. [PubMed: 11419452]
37. Wechsler, D. Manual for the Wechsler Adult Intelligence Scale. New York: The Psychological Corporation; 1955.
38. Raven, J.; Raven, J.; Court, J. Manual for Raven's Progressive Matrices and Vocabulary Scales. Oxford: Oxford Psychologists Press, Ltd; 1998.
39. Timm, NH. Applied Multivariate Analysis. New York: Springer-Verlag; 2002.
40. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009; 338:b2393.10.1136/bmj.b2393 [PubMed: 19564179]
41. Rubin, DB. Multiple Imputation for Nonresponse in Surveys. New York: J Wiley & Sons; 1987.
42. Richardson GA, Ryan C, Willford J, Day NL, Goldschmidt L. Prenatal alcohol and marijuana exposure: effects on neuropsychological outcomes at 10 years. Neurotoxicol Teratol. 2002; 24(3): 309–320. [PubMed: 12009486]
43. Sayal K, Heron J, Golding J, Alati R, Smith GD, Gray R, et al. Binge pattern of alcohol consumption during pregnancy and childhood mental health outcomes: longitudinal population-based study. Pediatrics. 2009; 123(2):e289–e296. [PubMed: 19171582]
44. Jepsen JRM, Fagerlund B, Mortensen EL. Do attention deficits influence IQ assessment in children and adolescents with ADHD? J Atten Disord. 2008; 12(6):551–561. [PubMed: 18815437]
45. Bradley RH, Whiteside L, Caldwell BM. Maternal IQ, the Home Environment, and Child IQ in Low Birthweight, Premature Children. Int J Behav Develop. 1993; 16(1):61–74.
46. Ebrahim SH, Diekman ST, Floyd RL, Decoufle P. Comparison of binge drinking among pregnant and nonpregnant women, United States, 1991–1995. Am J Obstet Gynecol. 1999; 180(1 Pt 1):1–7. [PubMed: 9914568]
47. Floyd RL, Decoufle P, Hungerford DW. Alcohol use prior to pregnancy recognition. Am J Prev Med. 1999; 17(2):101–107. [PubMed: 10490051]
48. Strandberg-Larsen K, Nielsen NR, Andersen A-MN, Olsen J, Grønbæk M. Characteristics of women who binge drink before and after they become aware of their pregnancy. Eur J Epidemiol. 2008; 23:565–572. [PubMed: 18553140]
49. Verkerk PH. The impact of alcohol misclassification on the relationship between alcohol and pregnancy outcome. Int J Epidemiol. 1992; 21 (Suppl 1):S33–7. [PubMed: 1399217]
50. Nybo Andersen AM, Olsen J. Do interviewers' health beliefs and habits modify responses to sensitive questions? A study using data Collected from pregnant women by means of computer-assisted telephone interviews. Am J Epidemiol. 2002; 155(1):95–100. [PubMed: 11772790]
51. Kesmodel U, Kesmodel PS. Drinking during pregnancy: attitudes and knowledge among pregnant Danish women, 1998. Alcohol Clin Exp Res. 2002; 26(10):1553–1560. [PubMed: 12394289]

52. Kesmodel US, Kesmodel PS. Alcohol in pregnancy: attitudes, knowledge and information practice among midwives in Denmark 2000 to 2009. Alcohol Clin Exp Res. 2011; 35(12):2226–2230. [PubMed: 21689120]

53. Guralnick MJ. A developmental systems model for early intervention. Infant Young Child. 2001; 14(2):1–18.

54. Streissguth, AP.; Bookstein, FL.; Barr, HM. A dose-response study of the enduring effects of prenatal alcohol-exposure: birth to 14 years. In: Spohr, H-L.; Steinhausen, H-C., editors. Alcohol, Pregnancy and the Developing Child. Cambridge: Cambridge University Press; 1996.

Table 1

Maternal Drinking Patterns and Distribution of Participants, Lifestyle During Pregnancy Study, Denmark, 2003–2008.

Cat	Average number of drinks/week		Binge drinking Weeks of pregnancy				Number in DNBC	Number Sampled	Sampling Fraction	Number Tested
	Before pregnancy	In pregnancy	1–2	3–4	5–8	9+				
1	N.a.	0	no	no	no	no	39004	579	0.015	257
1a	N.a.	0	yes	no	no	no	2098	203	0.097	113
1b	N.a.	0	no	yes	no	no	4006	217	0.054	104
1c	N.a.	0	no	no	yes	no	1400	200	0.143	109
1d	N.a.	0	no	no	no	yes	399	198	0.496	94
2	N.a.	1–4	no	no	no	no	26851	316	0.012	155
2a	N.a.	1–4	yes	no	no	no	1901	203	0.107	113
2b	N.a.	1–4	no	yes	no	no	4143	215	0.052	120
2c	N.a.	1–4	no	no	yes	no	1443	199	0.138	93
2d	N.a.	1–4	no	no	no	yes	901	205	0.228	114
3a	N.a.	0	— yes in at least 2 —				1919	153	0.080	81
3b	N.a.	1–8	— yes in at least 2 —				2905	160	0.055	82
			1–2	3–4	5 +					
4	N.a.	5–8	no	no	no		432	148	0.343	79
4a	N.a.	5–8	yes	no	no		31	25	0.806	11
4b	N.a.	5–8	no	yes	no		85	65	0.765	37
4c	N.a.	5–8	no	no	yes		125	82	0.056	40
5a	N.a.	≥9	no	no	no		20	19	0.950	15
5b	N.a.	≥9	yes in at least 2				19	11	0.679	5
6	0	0	no	no	no		10367	143	0.014	69
7	≥15	N.a.					974	146	0.150	85

Table 2

Missing value pattern. X designates full information, O designates missing information on one variable within column; (N=1628). Denmark, 2003–2008.

		Missing information on			
Number of variables with missing information	**N**	**WPPSI-R**	**TEACh-5**	**BRIEF***	**Covariates†**
0	1337	X	X	X	X
1	39	X	X	X	O
	2	X	X	O	X
	229	X	O	X	X
2	12	X	O	X	O
	1	X	O	O	X
	1	O	X	X	O
	1	O	O	X	X
3	6	O	O	X	O

*BRIEF – version for parent

†At least one covariate with missing information

Table 3

Correlation matrices for main outcomes. Denmark, 2003–2008.

Observed, pair-wise correlation matrix (95% CI), complete case, N = 1337					
		WPPSI-R		**TEACh-5**	**BRIEF (parent)**
WPPSI-R		1			
TEACh-5	0.49	(0.43 – 0.55)*		1	
BRIEF (parent)	−0.16	(−0.25 – −0.08)	−0.05	(−0.15 – 0.05)	1
Correlation matrix, adjusted for alcohol and core confounders (95% CI), complete case, N = 1337					
		WPPSI-R		**TEACh-5**	**BRIEF (parent)**
WPPSI-R		1			
TEACh-5	0.44	(0.38 – 0.50)		1	
BRIEF (parent)	−0.11	(−0.21 – −0.02)	−0.03	(−0.12 – 0.06)	1
Correlation matrix, adjusted for alcohol and core confounders (95% CI), imputed dataset, N = 1628					
		WPPSI-R		**TEACh-5**	**BRIEF (parent)**
WPPSI-R		1			
TEACh-5	0.52	(0.47 – 0.58)		1	
BRIEF (parent)	−0.17	(−0.25 – −0.10)	−0.08	(−0.17 – 0.01)	1

* Confidence intervals computed by bootstrap

BJOG. Author manuscript; available in PMC 2015 May 18.

Table 4

Mean differences between maternal alcohol intake in pregnancy and the reference group on WPPSI-R[*] intelligence test, TEACh-5[†] test of attention, and BRIEF[‡] test of executive function. Imputed data set analyses (N=1628). Denmark, 2003–2008.

		WPPSI-R[*]		TEACh-5[†]		BRIEF (parent)[‡]	
		Mean difference	**95% CI**	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**
				Unadjusted[#]			
				Multivariate test of no alcohol effect: p=0.44[††]			
Average alcohol intake				Multivariate test of no average alcohol effect: p=0.63[‡‡]			
0	758	*Reference*		*Reference*		*Reference*	
1–4	675	0. 84	(−1.30; 2.98)	0.02	(−0.14; 0.17)	0.81	(−0.76; 2.38)
5–8	175	−1.02	(−3.87; 1.82)	−0.01	(−0.30; 0.27)	0.63	(−2.37; 3.64)
≥9	20	−6.71	(−15.07; 1.65)	−0.57	(−1.25; 0.10)	2.04	(−0.87; 4.95)
Binge drinking				Multivariate test of no binge alcohol effect: p=0.28[##]			
No	495	*Reference*		*Reference*		*Reference*	
Yes	1133	1.27	(−0.42; 2.97)	0.04	(−0.09; 0.17)	0.61	(−0.64; 1.87)
				Adjusted for core confounders[§]			
				Multivariate test of no alcohol effect: p=0.80[††]			
Average alcohol intake				Multivariate test of no average alcohol effect: p=0.65 [‡‡]			
0	758	*Reference*		*Reference*		*Reference*	
1–4	675	0.45	(−1.44; 2.33)	0.01	(−0.14; 0.17)	0.81	(−0.63; 2.24)
5–8	175	−0.62	(−3.49; 2.25)	−0.00	(−0.27; 0.27)	0.09	(−2.56; 2.74)
≥9	20	−6.65	(−14.88; 1.59)	−0.60	(−1.28; 0.07)	0.64	(−2.35; 3.63)
Binge drinking				Multivariate test of no binge alcohol effect: p=0.90[##]			
No	495	*Reference*		*Reference*		*Reference*	
Yes	1133	0.32	(−1.13; 1.76)	−0.01	(−0.13; 0.12)	0.27	(−0.91; 1.44)
				Adjusted for all potential confounders[**]			
				Multivariate test of no alcohol effect: p=0.89[††]			
Average alcohol intake				Multivariate test of no average alcohol effect: p=0.74[‡‡]			
0	758	*Reference*		*Reference*		*Reference*	

		WPPSI-R*		TEACh-5†		BRIEF (parent)‡	
		Mean difference	**95% CI**	**Mean difference**	**95% CI**	**Mean difference**	**95% CI**
1–4	675	0.59	(−1.27; 2.44)	0.04	(−0.11; 0.19)	0.89	(−0.54; 2.31)
5–8	175	−0.41	(−3.20; 2.37)	0.03	(−0.26; 0.31)	−0.02	(−2.56; 2.51)
≥9	20	−5.53	(−13.87; 2.81)	−0.48	(−1.15; 0.19)	0.36	(−2.70; 3.42)
Binge drinking		Multivariate test of no binge alcohol effect: p=0.96##					
No	495	*Reference*		*Reference*		*Reference*	
Yes	1133	0.16	(−1.31; 1.64)	−0.01	(−0.14; 0.11)	0.17	(−1.01; 1.35)

*Full scale IQ

†Mean attention score

‡GEC Index

#Average alcohol intake adjusted for binge drinking and vice versa

§Adjusted for parental education, maternal IQ, prenatal maternal smoking, the child's gender and age at testing and tester

**Adjusted for parental education, maternal IQ, prenatal maternal smoking, the child's gender and age at testing and tester, parity, maternal marital status, age, BMI, prenatal maternal average number of drinks per week, home environment, postnatal parental smoking, health status, hearing and vision abilities

††Multivariate test of no alcohol effect (average or binge) across the three outcomes

‡‡Multivariate test of no average alcohol effect across the three outcomes

##Multivariate test of no binge alcohol effect across the three outcomes